

For the sake of advancing the application to allowance, Applicants have selected a specific embodiment of the claimed invention to pursue. Accordingly, claims 1-10, 15-19, 22, 24-26, 28 and 30-32 have been canceled. New claims 36-45 have been added. Upon entry of the Amendment, claims 29 and 33-45 are pending. Each of the claims presented for examination is characterized by a bile acid binder which is coating layered for targeted release in the colon..

New claims 36-38 correspond to cancelled claims 30-32 which have been re-written to depend on the independent formulation claims. Support for new claims 39-40 is found in the specification at page 6, lines 10-12. New claims 41-45 are identical to claims 36-40 but depend on the independent method of treatment claims. As such, no new matter has been introduced by any of the claim amendments.

Applicants submit that the cancellation of claims was not done in acquiescence of any objection or rejection relating to patentability. Rather, the claims were canceled and amended to advance the application to allowance so that Applicants may enjoy the benefits, without delay, conferred by a U.S. patent for allowable subject. Applicants reserve the right to file one or more continuation applications to defend the patentability of patentable subject matter that may have been removed by the claim amendments.

### III. Office Action

#### A. Restriction Requirement

The restriction requirement has been made final and, therefore, claim 35 continues to be withdrawn from consideration. For the following reasons, Applicants respectfully request the

Examiner to reconsider the restriction of claim 35 and to rejoin claim 35 in the present application.

Each of claims 29 and 33-45 is linked by the same technical feature that patentably distinguishes the claimed invention over the prior art. Specifically, claims 29 and 33-45 are characterized by a bile acid binder which is coating layered for the targeted release of the bile acid binder in the colon. As such, the bile acid binder is not administered for its cholesterol lowering effect. That is the therapeutic purpose of the IBAT inhibitor. In fact, the bile acid binder of the claimed invention is not formulated to function in the ileum as an anti-hyperlipidaemic agent.

Under normal circumstances, more than 90% of bile acids are reabsorbed in the small intestine during "enterohepatic circulation", i.e., the recurrent cycle in which bile salts and other substances excreted by the liver pass through the intestinal mucosa and become reabsorbed by the hepatic cells and re-excreted. Bile acid binders, such as cholestyramine or cholestipol, work to reduce plasma-LDL cholesterol by binding bile acids and bile salts in the small intestine, thereby interrupting the cycle of enterohepatic circulation. Bile acids are thus prevented from returning to the liver because the binder-bile acid complex is excreted in the faeces. In this regard, Applicants are submitting a copy of Lippincott's Illustrated Reviews, Pharmacology 2<sup>nd</sup> Ed., pp.210-212, under separate cover of the supplemental Information Disclosure Statement filed concurrently with this communication.

Rather, in the present invention, the delivery of the bile acid binder to the colon neither (i) affects the enterohepatic circulation of bile acids and bile salts nor (ii) causes a decrease in plasma LDL cholesterol. Therefore, as claimed, the bile acid binder does not have an anti-hyperlipidaemic effect. The sole purpose of delivering the bile acid binder to the colon is to bind

to bile acids and bile salts to decrease gastrointestinal side-effects, e.g., diarrhea, caused by an increased concentration of bile acids in colon following administration of the IBAT inhibitor. This is not taught in any of the references cited.

Thus, contrary to the prior art, the bile acid binder is present in the claimed formulation and administered for the prophylactic or therapeutic treatment of diarrhea during administration of the IBAT inhibitor. As set forth in the specification at page 5, lines 14-21:

If the transport of bile acids is blocked by an IBAT inhibitor the bile acid inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea – by irritation and inflammation – as a undesired side effect caused by the treatment with an IBAT inhibitor.

Another aspect of the provided combination therapy is that bile acid binder...could preferably be administered in a dosage form with colon release of the bile acid binder.

In view of the technical feature shared by claims 29 and 33-45, i.e., colonic release of the bile acid binder to prevent or treat diarrhea during IBAT administration, Applicants request the Examiner to withdraw the restriction requirement with respect to claim 35 and to examine claim 35 in the present application.

#### **B. Claim Rejection – 35 U.S.C. §103**

The prior art rejection of record was maintained in the final Office Action. Claims 1-10, 15-19, and 24-26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over US 5,723,458 to Brieaddy et al. ("Bricaddy") in view of US 5,614,220 to Hirakawa et al. ("Hirakawa") and US 5,659,027 to Spielvogel et al. ("Spielvogel").

The primary reference to Brieaddy allegedly discloses the use of IBAT inhibitor compounds in the treatment of hypercholesterolemia. Hirakawa allegedly discloses targeted release formulations. Spielvogel is cited for the alleged disclosure of combining hypercholesterolemic drugs with bile acid resins.

For the reasons of record, Applicants submit that the cited prior art, whether taken alone or in combination, does not teach or suggest the claimed formulation and method of treatment wherein a bile acid binder is coating layered for targeted release in the colon to prevent or treat diarrhea during administration of an IBAT inhibitor. The secondary reference to Hirakawa discloses that it is possible to obtain a pharmaceutical preparation wherein release of a medicinal active ingredient is intended to occur at the lower ileum, the ascending colon or the transverse colon (col. 4, lines 14-18). None of the medicinal active ingredients disclosed by Hirakawa include a bile acid binder which is coating layered for the targeted release in the colon (col. 4, lines 24-37).

Thus, Hirakawa suggests a pharmaceutical formulation providing the targeted release of one active ingredient. Therefore, there is no suggestion by Hirakawa of the claimed formulation comprising two active ingredients wherein the active ingredients are released in different locations of the digestive tract for different therapeutic purposes. Advantageously, the claimed formulation provides for a combination therapy for treating hypercholesterolemia and diarrhea during administration during administration of the IBAT inhibitor compound.

The specification provides an enabling disclosure for obtaining delivery of the bile acid binder to the colon. Examples of technologies to obtain such a delivery is provided by the publication cited on page 9, lines 1-2 of the specification, i.e., Watts, Peter J. et al., "Colonic Drug Delivery", Drug Development and Industrial Pharmacy, 23(9), 893-913 (1997). A copy of

Watts et al. is being submitted under separate cover of the supplemental Information Disclosure Statement filed concurrently with this communication..

For all of the foregoing reason including Applicants' remarks set forth in the previously filed communications, withdrawal of the §103 rejection with respect to claims 29-35 is requested.

### CONCLUSION

Upon entry of this Amendment, claims 29 and 33-45 are pending. Applicants respectfully submit that claims 29 and 33-45 are in condition for allowance, which action is earnestly solicited.

The Assistant Commissioner is hereby authorized to charge any fee due in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,

  
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Amended claims 29 and 33-35 -Version With Markings to Show Changes Made:

29. (Amended) A pharmaceutical formulation [for the prophylactic or the therapeutic treatment of hypercholesterolemia,] comprising therapeutically effective amounts of an IBAT inhibitor compound and a bile acid binder, wherein the [formulation is formulated to release the ] bile acid binder is coating layered for targeted release of the bile acid binder in the colon.

33. (Amended) A pharmaceutical formulation [for the prophylactic or the therapeutic treatment of hypercholesterolemia,] comprising therapeutically effective amounts of IBAT inhibitor compound and a bile acid binder, wherein the formulation is coating layered for targeted release of [formulated to release] the IBAT inhibitor compound in the ileum and the bile acid binder in the colon.

34. (Amended) A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to [ ,] hypercholesterolemia, wherein the method comprises [comprising] administering to the subject a therapeutically effective amount of an IBAT inhibitor compound and a bile acid binder, wherein the bile acid binder is administered for the prophylactic or therapeutic treatment of diarrhea during administration of the IBAT inhibitor [the pharmaceutical formulation according to any one of claims 29-33].

35. (Amended) A method for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhea during administration of an IBAT inhibitor compound, comprising administering to the subject a therapeutically effective amount of a bile acid binder, wherein the bile acid binder is coating layered for targeted release in the colon [the pharmaceutical formulation according to any one of claims 29-33].